<110> Davis, Samuel et al.

<120> Tie-2 Ligands, Methods of Making and Uses Thereof

<130> REG 330G1Z

<140> Not Yet Known
<141> Filed Herewith

<150> 09/442,717
<151> 1999-11-18

<150> 08/930,721
<151> 1998-03-10

<150> PCT/US96/04806
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<170> PatentIn Ver. 2.0

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ctagttttag aggtcagaag aaaggagcaa gttttgcgag aggcacggaa ggagtgtgct 300

ggcagtaca atg aca gtt ttc ctt tcc ttt gct ttc ctc gct gcc att ctg 351
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Leu Pro Glu His Asp Gly Asn Cys Arg Glu Ser Thr Thr Asp Gln Tyr
            50                  55                  60


aac aca aac gct ctg cag aga gat gct cca cac gtg gaa ccg gat ttc    543
Asn Thr Asn Ala Leu Gln Arg Asp Ala Pro His Val Glu Pro Asp Phe
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tct tcc cag aaa ctt caa cat ctg gaa cat gtg atg gaa aat tat act    591
Ser Ser Gln Lys Leu Gln His Leu Glu His Val Met Glu Asn Tyr Thr
        80                  85                  90


cag tgg ctg caa aaa ctt gag aat tac att gtg gaa aac atg aag tcg    639
Gln Trp Leu Gln Lys Leu Glu Asn Tyr Ile Val Glu Asn Met Lys Ser
    95                  100                 105                 110


gag atg gcc cag ata cag cag aat gca gtt cag aac cac acg gct acc    687
Glu Met Ala Gln Ile Gln Gln Asn Ala Val Gln Asn His Thr Ala Thr
                115                 120                 125


atg ctg gag ata gga acc agc ctc ctc tct cag act gca gag cag acc    735
Met Leu Glu Ile Gly Thr Ser Leu Leu Ser Gln Thr Ala Glu Gln Thr
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aga aag ctg aca gat gtt gag acc cag gta cta aat caa act tct cga    783
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ctt gag ata cag ctg ctg gag aat tca tta tcc acc tac aag cta gag      831
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aag caa ctt ctt caa cag aca aat gaa atc ttg aag atc cat gaa aaa      879
Lys Gln Leu Leu Gln Gln Thr Asn Glu Ile Leu Lys Ile His Glu Lys
175             180             185             190


aac agt tta tta gaa cat aaa atc tta gaa atg gaa gga aaa cac aag      927
Asn Ser Leu Leu Glu His Lys Ile Leu Glu Met Glu Gly Lys His Lys
            195             200             205


gaa gag ttg gac acc tta aag gaa gag aaa gag aac ctt caa ggc ttg      975
Glu Glu Leu Asp Thr Leu Lys Glu Glu Lys Glu Asn Leu Gln Gly Leu
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Val Thr Arg Gln Thr Tyr Ile Ile Gln Glu Leu Glu Lys Gln Leu Asn
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aga gct acc acc aac aac agt gtc ctt cag aag cag caa ctg gag ctg     1071
Arg Ala Thr Thr Asn Asn Ser Val Leu Gln Lys Gln Gln Leu Glu Leu
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atg gac aca gtc cac aac ctt gtc aat ctt tgc act aaa gaa ggt gtt     1119
Met Asp Thr Val His Asn Leu Val Asn Leu Cys Thr Lys Glu Gly Val
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gca gat gta tat caa gct ggt ttt aat aaa agt gga atc tac act att   1215
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tat att aat aat atg cca gaa ccc aaa aag gtg ttt tgc aat atg gat   1263
Tyr Ile Asn Asn Met Pro Glu Pro Lys Lys Val Phe Cys Asn Met Asp
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gtc aat ggg gga ggt tgg act gta ata caa cat cgt gaa gat gca agt   1311
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335   340   345   350

ccc tcc ggt gaa tat tgg ctg ggg aat gag ttt att ttt gcc att acc   1407
Pro Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe Ile Phe Ala Ile Thr
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agt cag agg cag tac atg cta aga att gag tta atg gac tgg gaa ggg   1455
Ser Gln Arg Gln Tyr Met Leu Arg Ile Glu Leu Met Asp Trp Glu Gly
            370   375   380

aac cga gcc tat tca cag tat gac aga ttc cac ata gga aat gaa aag   1503
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cag agc agc ctg atc tta cac ggt gct gat ttc agc act aaa gat gct    1599
Gln Ser Ser Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys Asp Ala
415             420             425             430


gat aat gac aac tgt atg tgc aaa tgt gcc ctc atg tta aca gga gga    1647
Asp Asn Asp Asn Cys Met Cys Lys Cys Ala Leu Met Leu Thr Gly Gly
            435             440             445


tgg tgg ttt gat gct tgt ggc ccc tcc aat cta aat gga atg ttc tat    1695
Trp Trp Phe Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Phe Tyr
            450             455             460


act gcg gga caa aac cat gga aaa ctg aat ggg ata aag tgg cac tac    1743
Thr Ala Gly Gln Asn His Gly Lys Leu Asn Gly Ile Lys Trp His Tyr
            465             470             475


ttc aaa ggg ccc agt tac tcc tta cgt tcc aca act atg atg att cga    1791
Phe Lys Gly Pro Ser Tyr Ser Leu Arg Ser Thr Thr Met Met Ile Arg
    480             485             490


cct tta gat ttt tgaaagcgca atgtcagaag cgattatgaa agcaacaaag        1843
Pro Leu Asp Phe
495


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tggagccgtt tgagttcaca agagtctcta cttggggtga cagtgctcac gtggctcgac 2023

tatagaaaac tccactgact gtcgggcttt aaaaagggaa gaaactgctg agcttgctgt 2083

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Tyr Asn Arg Ile Gln His Gly Gln Cys Ala Tyr Thr Phe Ile Leu Pro

        35   40   45

Glu His Asp Gly Asn Cys Arg Glu Ser Thr Thr Asp Gln Tyr Asn Thr

    50   55   60

6

Asn Ala Leu Gln Arg Asp Ala Pro His Val Glu Pro Asp Phe Ser Ser

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Gln Lys Leu Gln His Leu Glu His Val Met Glu Asn Tyr Thr Gln Trp

                     85   90   95

Leu Gln Lys Leu Glu Asn Tyr Ile Val Glu Asn Met Lys Ser Glu Met

               100   105   110

Ala Gln Ile Gln Gln Asn Ala Val Gln Asn His Thr Ala Thr Met Leu

               115   120   125

Glu Ile Gly Thr Ser Leu Leu Ser Gln Thr Ala Glu Gln Thr Arg Lys

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Leu Thr Asp Val Glu Thr Gln Val Leu Asn Gln Thr Ser Arg Leu Glu

145   150   155   160

Ile Gln Leu Leu Glu Asn Ser Leu Ser Thr Tyr Lys Leu Glu Lys Gln

               165   170   175

Leu Leu Gln Gln Thr Asn Glu Ile Leu Lys Ile His Glu Lys Asn Ser

               180   185   190

Leu Leu Glu His Lys Ile Leu Glu Met Glu Gly Lys His Lys Glu Glu

               195   200   205

Leu Asp Thr Leu Lys Glu Glu Lys Glu Asn Leu Gln Gly Leu Val Thr

           210   215   220

Arg Gln Thr Tyr Ile Ile Gln Glu Leu Glu Lys Gln Leu Asn Arg Ala
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Thr Thr Asn Asn Ser Val Leu Gln Lys Gln Gln Leu Glu Leu Met Asp
                245   250   255

Thr Val His Asn Leu Val Asn Leu Cys Thr Lys Glu Gly Val Leu Leu
                260   265   270

Lys Gly Gly Lys Arg Glu Glu Glu Lys Pro Phe Arg Asp Cys Ala Asp
                275   280   285

Val Tyr Gln Ala Gly Phe Asn Lys Ser Gly Ile Tyr Thr Ile Tyr Ile
                290   295   300

Asn Asn Met Pro Glu Pro Lys Lys Val Phe Cys Asn Met Asp Val Asn
305   310   315   320

Gly Gly Gly Trp Thr Val Ile Gln His Arg Glu Asp Ala Ser Leu Asp
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Phe Gln Arg Gly Trp Lys Glu Tyr Lys Met Gly Phe Gly Asn Pro Ser
                340   345   350

Gly Glu Tyr Trp Leu Gly Asn Glu Phe Ile Phe Ala Ile Thr Ser Gln
                355   360   365

Arg Gln Tyr Met Leu Arg Ile Glu Leu Met Asp Trp Glu Gly Asn Arg
                370   375   380

8

Ala Tyr Ser Gln Tyr Asp Arg Phe His Ile Gly Asn Glu Lys Gln Asn

385   390   395   400

Tyr Arg Leu Tyr Leu Lys Gly His Thr Gly Thr Ala Gly Lys Gln Ser

                405   410   415

Ser Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys Asp Ala Asp Asn

                420   425   430

Asp Asn Cys Met Cys Lys Cys Ala Leu Met Leu Thr Gly Gly Trp Trp

                435   440   445

Phe Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Phe Tyr Thr Ala

                450   455   460

Gly Gln Asn His Gly Lys Leu Asn Gly Ile Lys Trp His Tyr Phe Lys

465   470   475   480

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aaaattttaa aattttagaa caaagctaac aaatggctag ttttctatga ttcttcttca 180

aacgctttct ttgaggggga aagagtcaaa caaacaagca gttttacctg aaataaagaa 240

ctagttttag aggtcagaag aaaggagcaa gttttgcgag aggcacggaa ggagtgtgct 300

ggcagtaca atg aca gtt ttc ctt tcc ttt gct ttc ctc gct gcc att ctg 351
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           1   5   10

act cac ata ggg tgc agc aat cag cgc cga agt cca gaa aac agt ggg 399
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15   20   25   30

aga aga tat aac cgg att caa cat ggg caa tgt gcc tac act ttc att 447
Arg Arg Tyr Asn Arg Ile Gln His Gly Gln Cys Ala Tyr Thr Phe Ile

            35   40   45

ctt cca gaa cac gat ggc aac tgt cgt gag agt acg aca gac cag tac 495
Leu Pro Glu His Asp Gly Asn Cys Arg Glu Ser Thr Thr Asp Gln Tyr

           50   55   60

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aac aca aac gct ctg cag aga gat gct cca cac gtg gaa ccg gat ttc     543
Asn Thr Asn Ala Leu Gln Arg Asp Ala Pro His Val Glu Pro Asp Phe
         65                  70                  75


tct tcc cag aaa ctt caa cat ctg gaa cat gtg atg gaa aat tat act     591
Ser Ser Gln Lys Leu Gln His Leu Glu His Val Met Glu Asn Tyr Thr
      80                  85                  90


cag tgg ctg caa aaa ctt gag aat tac att gtg gaa aac atg aag tcg     639
Gln Trp Leu Gln Lys Leu Glu Asn Tyr Ile Val Glu Asn Met Lys Ser
 95                 100                 105                 110


gag atg gcc cag ata cag cag aat gca gtt cag aac cac acg gct acc     687
Glu Met Ala Gln Ile Gln Gln Asn Ala Val Gln Asn His Thr Ala Thr
                115                 120                 125


atg ctg gag ata gga acc agc ctc ctc tct cag act gca gag cag acc     735
Met Leu Glu Ile Gly Thr Ser Leu Leu Ser Gln Thr Ala Glu Gln Thr
                130                 135                 140


aga aag ctg aca gat gtt gag acc cag gta cta aat caa act tct cga     783
Arg Lys Leu Thr Asp Val Glu Thr Gln Val Leu Asn Gln Thr Ser Arg
           145                 150                 155


ctt gag ata cag ctg ctg gag aat tca tta tcc acc tac aag cta gag     831
Leu Glu Ile Gln Leu Leu Glu Asn Ser Leu Ser Thr Tyr Lys Leu Glu
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175   180   185   190

aac agt tta tta gaa cat aaa atc tta gaa atg gaa gga aaa cac aag   927
Asn Ser Leu Leu Glu His Lys Ile Leu Glu Met Glu Gly Lys His Lys
             195   200   205

gaa gag ttg gac acc tta aag gaa gag aaa gag aac ctt caa ggc ttg   975
Glu Glu Leu Asp Thr Leu Lys Glu Glu Lys Glu Asn Leu Gln Gly Leu
             210   215   220

gtt act cgt caa aca tat ata atc cag gag ctg gaa aag caa tta aac   1023
Val Thr Arg Gln Thr Tyr Ile Ile Gln Glu Leu Glu Lys Gln Leu Asn
             225   230   235

aga gct acc acc aac aac agt gtc ctt cag aag cag caa ctg gag ctg   1071
Arg Ala Thr Thr Asn Asn Ser Val Leu Gln Lys Gln Gln Leu Glu Leu
             240   245   250

atg gac aca gtc cac aac ctt gtc aat ctt tgc act aaa gaa gtt tta   1119
Met Asp Thr Val His Asn Leu Val Asn Leu Cys Thr Lys Glu Val Leu
255   260   265   270

cta aag gga gga aaa aga gag gaa gac aaa cca ttt aga gac tgt gca   1167
Leu Lys Gly Gly Lys Arg Glu Glu Asp Lys Pro Phe Arg Asp Cys Ala
             275   280   285

gat gta tat caa gct ggt ttt aat aaa agt gga atc tac act att tat   1215
Asp Val Tyr Gln Ala Gly Phe Asn Lys Ser Gly Ile Tyr Thr Ile Tyr
             290   295   300

att aat aat atg cca gaa ccc aaa aag gtg ttt tgc aat atg gat gtc   1263
Ile Asn Asn Met Pro Glu Pro Lys Lys Val Phe Cys Asn Met Asp Val
        305   310   315

aat ggg gga ggt tgg act gta ata caa cat cgt gaa gat gga agt cta   1311
Asn Gly Gly Gly Trp Thr Val Ile Gln His Arg Glu Asp Gly Ser Leu
    320   325   330

gat ttc caa aga ggc tgg aag gaa tat aaa atg ggt ttt gga aat ccc   1359
Asp Phe Gln Arg Gly Trp Lys Glu Tyr Lys Met Gly Phe Gly Asn Pro
335   340   345   350

tcc ggt gaa tat tgg ctg ggg aat gag ttt att ttt gcc att acc agt   1407
Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe Ile Phe Ala Ile Thr Ser
        355   360   365

cag agg cag tac atg cta aga att gag tta atg gac tgg gaa ggg aac   1455
Gln Arg Gln Tyr Met Leu Arg Ile Glu Leu Met Asp Trp Glu Gly Asn
        370   375   380

cga gcc tat tca cag tat gac aga ttc cac ata gga aat gaa aag caa   1503
Arg Ala Tyr Ser Gln Tyr Asp Arg Phe His Ile Gly Asn Glu Lys Gln
        385   390   395

aac tat agg ttg tat tta aaa ggt cac act ggg aca gca gga aaa cag   1551
Asn Tyr Arg Leu Tyr Leu Lys Gly His Thr Gly Thr Ala Gly Lys Gln
    400   405   410

13

agc agc ctg atc tta cac ggt gct gat ttc agc act aaa gat gct gat   1599
Ser Ser Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys Asp Ala Asp
415   420   425   430

aat gac aac tgt atg tgc aaa tgt gcc ctc atg tta aca gga gga tgg   1647
Asn Asp Asn Cys Met Cys Lys Cys Ala Leu Met Leu Thr Gly Gly Trp
            435   440   445

tgg ttt gat gct tgt ggc ccc tcc aat cta aat gga atg ttc tat act   1695
Trp Phe Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Phe Tyr Thr
            450   455   460

gcg gga caa aac cat gga aaa ctg aat ggg ata aag tgg cac tac ttc   1743
Ala Gly Gln Asn His Gly Lys Leu Asn Gly Ile Lys Trp His Tyr Phe
            465   470   475

aaa ggg ccc agt tac tcc tta cgt tcc aca act atg atg att cga cct   1791
Lys Gly Pro Ser Tyr Ser Leu Arg Ser Thr Thr Met Met Ile Arg Pro
            480   485   490

tta gat ttt tgaaagcgca atgtcagaag cgattatgaa agcaacaaag   1840
Leu Asp Phe
495

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tatagaaaac tccactgact gtcgggcttt aaaaagggaa gaaactgctg agcttgctgt 2080

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Tyr Asn Arg Ile Gln His Gly Gln Cys Ala Tyr Thr Phe Ile Leu Pro

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Glu His Asp Gly Asn Cys Arg Glu Ser Thr Thr Asp Gln Tyr Asn Thr

    50   55   60

Asn Ala Leu Gln Arg Asp Ala Pro His Val Glu Pro Asp Phe Ser Ser

65   70   75   80

Gln Lys Leu Gln His Leu Glu His Val Met Glu Asn Tyr Thr Gln Trp

                85   90   95

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Leu Gln Lys Leu Glu Asn Tyr Ile Val Glu Asn Met Lys Ser Glu Met
            100   105   110

Ala Gln Ile Gln Gln Asn Ala Val Gln Asn His Thr Ala Thr Met Leu
            115   120   125

Glu Ile Gly Thr Ser Leu Leu Ser Gln Thr Ala Glu Gln Thr Arg Lys
        130   135   140

Leu Thr Asp Val Glu Thr Gln Val Leu Asn Gln Thr Ser Arg Leu Glu
145   150   155   160

Ile Gln Leu Leu Glu Asn Ser Leu Ser Thr Tyr Lys Leu Glu Lys Gln
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Leu Leu Gln Gln Thr Asn Glu Ile Leu Lys Ile His Glu Lys Asn Ser
            180   185   190

Leu Leu Glu His Lys Ile Leu Glu Met Glu Gly Lys His Lys Glu Glu
            195   200   205

Leu Asp Thr Leu Lys Glu Glu Lys Glu Asn Leu Gln Gly Leu Val Thr
        210   215   220

Arg Gln Thr Tyr Ile Ile Gln Glu Leu Glu Lys Gln Leu Asn Arg Ala
225   230   235   240

Thr Thr Asn Asn Ser Val Leu Gln Lys Gln Gln Leu Glu Leu Met Asp
            245   250   255

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Thr Val His Asn Leu Val Asn Leu Cys Thr Lys Glu Val Leu Leu Lys
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            275                 280                 285

Tyr Gln Ala Gly Phe Asn Lys Ser Gly Ile Tyr Thr Ile Tyr Ile Asn
        290             295                 300

Asn Met Pro Glu Pro Lys Lys Val Phe Cys Asn Met Asp Val Asn Gly
305             310                 315                 320

Gly Gly Trp Thr Val Ile Gln His Arg Glu Asp Gly Ser Leu Asp Phe
            325                 330                 335

Gln Arg Gly Trp Lys Glu Tyr Lys Met Gly Phe Gly Asn Pro Ser Gly
            340                 345                 350

Glu Tyr Trp Leu Gly Asn Glu Phe Ile Phe Ala Ile Thr Ser Gln Arg
        355                 360                 365

Gln Tyr Met Leu Arg Ile Glu Leu Met Asp Trp Glu Gly Asn Arg Ala
        370             375                 380

Tyr Ser Gln Tyr Asp Arg Phe His Ile Gly Asn Glu Lys Gln Asn Tyr
385             390                 395                 400

Arg Leu Tyr Leu Lys Gly His Thr Gly Thr Ala Gly Lys Gln Ser Ser
            405                 410                 415
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Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys Asp Ala Asp Asn Asp
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Asn Cys Met Cys Lys Cys Ala Leu Met Leu Thr Gly Gly Trp Trp Phe
            435   440   445

Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Phe Tyr Thr Ala Gly
            450   455   460

Gln Asn His Gly Lys Leu Asn Gly Ile Lys Trp His Tyr Phe Lys Gly
465   470   475   480

Pro Ser Tyr Ser Leu Arg Ser Thr Thr Met Met Ile Arg Pro Leu Asp
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ccaagtgagc aggactgttc ttcccactgc aatctgacag tttactgcat gcctggagag 180

aacacagcag taaaaaccag gtttgctact ggaaaaagag gaaagagaag actttcattg 240

acggacccag ccatggcagc gtagcagccc tgcgtttcag acggcagcag ctcgggactc 300

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                5   10   15

gcc tat aac aac ttt cgg aag agc atg gac agc ata gga aag aag caa   455
Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys Gln
                20   25   30

tat cag gtc cag cat ggg tcc tgc agc tac act ttc ctc ctg cca gag   503
Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro Glu
        35   40   45

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Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala Val
50   55   60   65

cag agg gac gcg ccg ctc gaa tac gat gac tcg gtg cag agg ctg caa   599
Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu Gln

19

gtg ctg gag aac atc atg gaa aac aac act cag tgg cta atg aag ctt   647
Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys Leu
            85   90   95

gag aat tat atc cag gac aac atg aag aaa gaa atg gta gag ata cag   695
Glu Asn Tyr Ile Gln Asp Asn Met Lys Lys Glu Met Val Glu Ile Gln
            100   105   110

cag aat gca gta cag aac cag acg gct gtg atg ata gaa ata ggg aca   743
Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Ile Glu Ile Gly Thr
            115   120   125

aac ctg ttg aac caa aca gct gag caa acg cgg aag tta act gat gtg   791
Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp Val
130   135   140   145

gaa gcc caa gta tta aat cag acc acg aga ctt gaa ctt cag ctc ttg   839
Glu Ala Gln Val Leu Asn Gln Thr Thr Arg Leu Glu Leu Gln Leu Leu
            150   155   160

gaa cac tcc ctc tcg aca aac aaa ttg gaa aaa cag att ttg gac cag   887
Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Ile Leu Asp Gln
            165   170   175

acc agt gaa ata aac aaa ttg caa gat aag aac agt ttc cta gaa aag   935
Thr Ser Glu Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu Lys
            180   185   190

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aag gtg cta gct atg gaa gac aag cac atc atc caa cta cag tca ata    983
Lys Val Leu Ala Met Glu Asp Lys His Ile Ile Gln Leu Gln Ser Ile
    195             200             205


aaa gaa gag aaa gat cag cta cag gtg tta gta tcc aag caa aat tcc    1031
Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn Ser
210             215             220             225


atc att gaa gaa cta gaa aaa aaa ata gtg act gcc acg gtg aat aat    1079
Ile Ile Glu Glu Leu Glu Lys Lys Ile Val Thr Ala Thr Val Asn Asn
            230             235             240


tca gtt ctt caa aag cag caa cat gat ctc atg gag aca gtt aat aac    1127
Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn Asn
            245             250             255


tta ctg act atg atg tcc aca tca aac tca gct aag gac ccc act gtt    1175
Leu Leu Thr Met Met Ser Thr Ser Asn Ser Ala Lys Asp Pro Thr Val
        260             265             270


gct aaa gaa gaa caa atc agc ttc aga gac tgt gct gaa gta ttc aaa    1223
Ala Lys Glu Glu Gln Ile Ser Phe Arg Asp Cys Ala Glu Val Phe Lys
    275             280             285


tca gga cac acc aca aat ggc atc tac acg tta aca ttc cct aat tct    1271
Ser Gly His Thr Thr Asn Gly Ile Tyr Thr Leu Thr Phe Pro Asn Ser
290             295             300             305


aca gaa gag atc aag gcc tac tgt gac atg gaa gct gga gga ggc ggg    1319
Thr Glu Glu Ile Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly Gly Gly
            310             315             320
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tgg aca att att cag cga cgt gag gat ggc agc gtt gat ttt cag agg    1367
Trp Thr Ile Ile Gln Arg Arg Glu Asp Gly Ser Val Asp Phe Gln Arg
        325               330               335


act tgg aaa gaa tat aaa gtg gga ttt ggt aac cct tca gga gaa tat    1415
Thr Trp Lys Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly Glu Tyr
        340               345               350


tgg ctg gga aat gag ttt gtt tcg caa ctg act aat cag caa cgc tat    1463
Trp Leu Gly Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln Arg Tyr
        355               360               365


gtg ctt aaa ata cac ctt aaa gac tgg gaa ggg aat gag gct tac tca    1511
Val Leu Lys Ile His Leu Lys Asp Trp Glu Gly Asn Glu Ala Tyr Ser
370               375               380               385


ttg tat gaa cat ttc tat ctc tca agt gaa gaa ctc aat tat agg att    1559
Leu Tyr Glu His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr Arg Ile
                390               395               400


cac ctt aaa gga ctt aca ggg aca gcc ggc aaa ata agc agc atc agc    1607
His Leu Lys Gly Leu Thr Gly Thr Ala Gly Lys Ile Ser Ser Ile Ser
        405               410               415


caa cca gga aat gat ttt agc aca aag gat gga gac aac gac aaa tgt    1655
Gln Pro Gly Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp Lys Cys
        420               425               430
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att tgc aaa tgt tca caa atg cta aca gga ggc tgg tgg ttt gat gca   1703
Ile Cys Lys Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe Asp Ala
    435   440   445

tgt ggt cct tcc aac ttg aac gga atg tac tat cca cag agg cag aac   1751
Cys Gly Pro Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg Gln Asn
450   455   460   465

aca aat aag ttc aac ggc att aaa tgg tac tac tgg aaa ggc tca ggc   1799
Thr Asn Lys Phe Asn Gly Ile Lys Trp Tyr Tyr Trp Lys Gly Ser Gly
                470   475   480

tat tcg ctc aag gcc aca acc atg atg atc cga cca gca gat ttc   1844
Tyr Ser Leu Lys Ala Thr Thr Met Met Ile Arg Pro Ala Asp Phe
            485   490   495

taaacatccc agtccacctg aggaactgtc tcgaactatt ttcaaagact taagcccagt 1904

gcactgaaag tcacggctgc gcactgtgtc ctcttccacc acagagggcg tgtgctcggt 1964

gctgacggga cccacatgct ccagattaga gcctgtaaac tttatcactt aaacttgcat 2024

cacttaacgg accaaagcaa gaccctaaac atccataatt gtgattagac agaacaccta 2084

tgcaaagatg aacccgaggc tgagaatcag actgacagtt tacagacgct gctgtcacaa 2144

ccaagaatgt tatgtgcaag tttatcagta aataactgga aaacagaaca cttatgttat 2204

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cccatatgtc ctgaattc   2282

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Met Trp Gln Ile Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala

1   5   10   15

Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys

            20   25   30

Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro

        35   40   45

Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala

    50   55   60

Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu

65   70   75   80

Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys

                85   90   95

Leu Glu Asn Tyr Ile Gln Asp Asn Met Lys Lys Glu Met Val Glu Ile

            100   105   110

Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Ile Glu Ile Gly
      115   120   125

Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp
      130   135   140

Val Glu Ala Gln Val Leu Asn Gln Thr Thr Arg Leu Glu Leu Gln Leu
145   150   155   160

Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Ile Leu Asp
            165   170   175

Gln Thr Ser Glu Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu
            180   185   190

Lys Lys Val Leu Ala Met Glu Asp Lys His Ile Ile Gln Leu Gln Ser
        195   200   205

Ile Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn
      210   215   220

Ser Ile Ile Glu Glu Leu Glu Lys Lys Ile Val Thr Ala Thr Val Asn
225   230   235   240

Asn Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn
            245   250   255

Asn Leu Leu Thr Met Met Ser Thr Ser Asn Ser Ala Lys Asp Pro Thr
        260   265   270

Val Ala Lys Glu Glu Gln Ile Ser Phe Arg Asp Cys Ala Glu Val Phe
        275   280   285

Lys Ser Gly His Thr Thr Asn Gly Ile Tyr Thr Leu Thr Phe Pro Asn
    290   295   300

Ser Thr Glu Glu Ile Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly Gly
305   310   315   320

Gly Trp Thr Ile Ile Gln Arg Arg Glu Asp Gly Ser Val Asp Phe Gln
                325   330   335

Arg Thr Trp Lys Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly Glu
            340   345   350

Tyr Trp Leu Gly Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln Arg
        355   360   365

Tyr Val Leu Lys Ile His Leu Lys Asp Trp Glu Gly Asn Glu Ala Tyr
    370   375   380

Ser Leu Tyr Glu His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr Arg
385   390   395   400

Ile His Leu Lys Gly Leu Thr Gly Thr Ala Gly Lys Ile Ser Ser Ile
                405   410   415

Ser Gln Pro Gly Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp Lys
            420   425   430

26

Cys Ile Cys Lys Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe Asp
        435   440   445

Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg Gln
        450   455   460

Asn Thr Asn Lys Phe Asn Gly Ile Lys Trp Tyr Tyr Trp Lys Gly Ser
465   470   475   480

Gly Tyr Ser Leu Lys Ala Thr Thr Met Met Ile Arg Pro Ala Asp Phe
                485   490   495